

PATENT SPECIFICATION

(11) 1 586 798

1 586 798

(21) Application No. 48781/77 (22) Filed 23 Nov. 1977
 (31) Convention Application No. Cl 1695
 (32) Filed 23 Nov. 1976 in
 (33) Hungary (HU)
 (44) Complete Specification published 25 March 1981
 (51) INT CL³ C07C 51/32 51/34/63/52 101/44
 (52) Index at acceptance
 C2C 220 226 227 22Y 30Y 311 313 31Y 322 32Y 338 364 366 367
 36Y 37X 409 490 620 624 628 658 660 662 680 697 699
 802 AA BU LT

(72) Inventors RUDOLF SZEBENI
 DEZSÖ KORBONITS
 ENDRE PALOSI
 CSABA GÖNCZI
 GERGELY HEJA
 ERZSEBET MOLNAR
 PAL KISS and
 IDA KANZEL

(54) PREPARATION OF OPTIONALLY SUBSTITUTED PHENYL- AND NAPHTHYL-ALKANOIC ACIDS

(71) We, CHINÓIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT., a body corporate organised under the laws of Hungary of 1—5 To.u., Budapest IV, 5 Hungary, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 The present invention relates to a new process for the preparation of optionally substituted phenyl- and naphthyl-alkanoic acids.

15 These compounds include therapeutically useful anti-inflammatory agents.

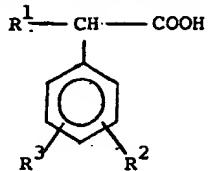
20 The preparation of compounds of this class has been disclosed in U.S. Patent Specification No. 3,600,437, German Patent Specification No. 1,941,625, in Belgian Patent Specifications Nos. 737,417 and 25 621,225, in British Patent Specifications Nos. 971,700, 1,132,318 and 1,552,202, in French Patent Specifications Nos. 1,549,728 and 1,545,270 and in Hungarian Patent Specifications Nos. 166,290 and 168,046.

30 The common feature of all the processes mentioned above is that during the preparation of the phenylalkanoic acid or the phenylalkyl cyanide from which the acid may be formed by hydrolysis, the critical step is the formation of the bond between the carbon atom of the carboxylic acid group and the alkyl group. These synthetic methods either succeed with a bad yield or give the desired product by complex processing of intermediate products which are difficult to purify.

35 40 The disadvantages may be eliminated by a synthetic method which does not involve

the bond problem of the carbon atom of the carboxylic acid. This problem is solved by the process disclosed in British Patent Specification No. 1,522,202, according to which as starting materials acetylenes are used which are converted to esters in the presence of alcohol with thallium [II] nitrate with isomerisation and, if desired, the alkoxy-carbonyl group is converted to a carboxylic group by hydrolysis.

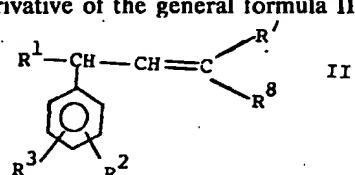
45 Our invention is directed to a process for the preparation of phenyl- and naphthyl-alkanoic acids of the general formula I



55 wherein

R¹ is hydrogen, C₁₋₄ alkyl or C₇₋₁₀ aralkyl,
 R² is hydrogen or halogen,

R³ is C₁₋₆ alkyl, C₇₋₁₀ aralkyl, phenyl, phenoxy, or —NH—R⁴ wherein R⁴ is a phenyl group optionally substituted with one or two halogen atoms; or
 R² and R³ may together form a fused benzene ring which may optionally be substituted with C₁₋₄ alkoxy group, which comprises oxidizing an alkene derivative of the general formula II



5	wherein R ¹ , R ² , R ³ , R ⁴ , R ⁵ , and R ⁶ are as defined above. R ⁷ and R ⁸ are hydrogen, C ₁₋₄ alkyl, C ₆₋₈ cycloalkyl or phenyl, or	70
10	R ⁷ and R ⁸ together with the carbon atom to which they are attached form a five- or six-membered ring. The substituents in the present invention mentioned below are always as defined above.	75
15	The products are produced according to the invention by oxidative splitting of the carbon-carbon double bond. The process may be performed on a large scale and the yield is very good.	80
20	According to the invention olefins of the general formula II are oxidized by chemical oxidizing agents, preferably by chromic acid or potassium permanganate or e.g. converted to an ozonide and the ozonide is decomposed by methods known <i>per se</i> . According to another method of the invention the oxidation may be carried out	85
25	with potassium permanganate in aqueous acetic acid at a temperature of 0 to 5°C, preferably at about 3°C or in the presence of sodium hydrogen carbonate in an organic solvent, preferably in acetone at 0 to 50°C, preferably at 7°C. The oxidation with potassium permanganate may also be performed in benzene if as crown complex forming agent e.g. dicyclohexyl-18-crown-6 is used. The oxidation may be carried out in	90
30	a homogeneous medium at 0—70°C, preferably at 25°C, when oxidation is completed within minutes.	95
35	A further preferred oxidation process is the employment of an oxidizing agent containing alkali metal periodate and alkali metal permanganate, e.g. 97.5% of sodium periodate and 2.5% potassium permanganate. As a solvent preferably tertiary butanol may be used. The oxidation is completed in 6 hours in an excellent, nearly quantitative yield.	100
40	According to another embodiment of the present invention the alkene derivative of the general formula II is oxidized with chromium trioxide.	105
45	The oxidation is completed in acetic acid at a temperature of 0 to 100°C, preferably at about 70°C within 1 hour.	110
50	The alkene derivatives of the general formula II may preferably be converted by saturation of the double bond with ozone and by decomposing the ozonide obtained. Through the solution of the olefin in e.g. chloroform, methylene chloride, acetic acid, or ethyl acetate oxygen saturated with ozone is introduced at a temperature of -50°C to -80°C, preferably at -78°C. In order to prevent polymerisation an acidic hydrolysing medium containing hydrogen peroxide is used. The acidic reaction	115
55		
60		
65		
	mixture is extracted with an organic solvent and after removing the organic layer the carboxylic acids of the general formula I, wherein the substituents are as defined above, may be separated or, if desired metal salts or acid addition salts may be formed by reaction with bases such as alkali metal hydroxides, alkaline earth metal hydroxides or nitrogen-containing organic bases in aqueous medium or a solvent medium by known techniques of salt formation and isolated by crystallization or by evaporation of the solvent.	
	The alkene derivatives used as starting materials may be conveniently prepared by Wittig reaction or by dehydrating the appropriate tertiary alcohols.	
	The invention is further illustrated by the following non-limiting Examples.	
	Examples	
	Example 1	
	188.23 g. (0.5 mole) of 1,1-diphenyl-3-(3-phenoxyphenyl)-1-butene are dissolved in 200 ml. of methylenechloride. the mixture is cooled to -78°C and ozonised oxygen is introduced into the mixture for 12 hours. After the introduction is completed, the solvent is removed and the residue is dissolved in 100 ml. of acetic acid. The obtained solution is added dropwise to a mixture of 114 g. of 30% hydrogen peroxide, 5 ml. of sulfuric acid and 200 ml. of water under cooling. After the addition is complete, the solution is further heated to boiling for 2 hours, cooled and extracted with 3x500 ml. diethyl ether. The ethereal layers are washed with sodium hydroxide and the aqueous solution is acidified followed by extraction with 3x500 ml. of diethyl ether. The extract is evaporated after drying and the residue is distilled off. The product obtained is 2-(3-phenoxyphenyl)-propionic acid.	
	Bp.: 190—192°C (0.4 mmHg). n _D ²⁵ =1.575	
	Example 2	
	Using the general method of Example 1, from 126.17 g. (0.5 mole) 1,1-dimethyl-3-(3-phenoxyphenyl)-1-butene, 2-(3-phenoxyphenyl)-propionic acid is obtained.	
	Example 3	
	From 146.2 g. (0.5 mole) 2 - (3-phenoxyphenyl) - 1 - cyclohexylidene - propane 2 - (3 - phenoxyphenyl) - propionic acid is obtained by the general method of Example 1.	
	Example 4	
	150.69 g. (0.5 mole) of 1 - phenyl - 3 - (3 - phenoxyphenyl) - 1 - butene is oxidised according to the general method of	125

Example 1, and thus 2 - (3 - phenoxyphenyl) - propionic acid is obtained.

Example 5

5 46.98 g. (0.125 mole) of 1,1 - diphenyl - 3 - phenoxyphenyl) - 1 - butene are dissolved in 500 ml. of acetic acid. 27 g. CrO_3 in 30 ml. of water is added dropwise to the solution at 70°C. After heating for 1 hour the acetic acid is removed and the residue is treated with 500 ml. sulfuric acid. The acidic solution is further worked up according to Example 1. 2 - (3 - phenoxyphenyl) - propionic acid of boiling point: 190—192°C (0.4 mmHg) is obtained.

Example 6

10 31.54 g. (0.125 mole) of 1,1 - dimethyl - 3 - (3 - phenoxyphenyl) - 1 - butene is oxidised by the method of Example 5. 2 - (3 - phenoxy - phenyl) - propionic acid is obtained.

Example 7

15 36.55 g. (0.125 mole) 2 - (3 - phenoxyphenyl) - 1 - cyclohexylidene - propane is oxidised by the method of Example 5 to 2 - (3 - phenoxy - phenyl) - propionic acid.

Example 8

20 37.67 g. (0.125 mole) of 1 - phenyl - 3 - (3 - phenoxyphenyl) - 1 - butene is oxidised by the method of Example 5 to yield 2 - (3 - phenoxyphenyl) - propionic acid.

Example 9

25 35 40 45 A mixture of 3.76 g. (0.01 mole) 1,1 - diphenyl - 3 - (3 - phenoxy - phenyl) - 1 - butene, 100 g. of ice-cold water and 420 g. acetic acid is stirred and 4.74 g. (0.03 mole) of potassium permanganate is added at such a rate that the temperature does not exceed 3°C. The mixture is filtered, alkalized, filtered and concentrated. After acidifying and working up the mixture according to Example 1, 2 - (3 - phenoxyphenyl) - propionic acid of boiling point of 190—192°C (0.4 mmHg) is obtained.

Example 10

50 55 60 2.52 g. (0.01 mole) of 1,1 - dimethyl - 3 - (3 - phenoxyphenyl) - 1 - butene is oxidised by the method of Example 9, and 2 - (3 - phenoxyphenyl) - 1 - butene is oxidised by the method of Example 9, and 2 - (3 - phenoxyphenyl) - propionic acid is obtained.

Example 11

2.92 g. (0.01 mole) 2 - (3 - phenoxyphenyl) - 1 - cyclohexylidene - propane is oxidised by the method of Example 9 to 2 - (3 - phenoxyphenyl) - propionic acid.

Example 12
Using the method of Example 9, 3.01 g. (0.01 mole) 1 - phenyl - 3 - (3 - phenoxyphenyl) - 1 - butene is used as starting material and thus 2 - (3 - phenoxyphenyl) - propionic acid is obtained.

Example 13

47.30 g. 1,1 - diphenyl - 3 - (2 - fluoro - 4 - biphenyl) - 1 - butene is dissolved in 500 ml. of acetic acid and 27 g. CrO_3 in 30 ml. of water is added dropwise at 70°C. The solution is heated for 1 hour. The acetic acid is removed and the residue is acidified. The acidic solution is extracted with chloroform. The chloroform solution is dried and evaporated. 2 - (2 - fluoro - 4 - biphenyl) - propionic acid is obtained, melting point: 110—111°C.

Example 14

To a mixture of 3.64 g. (0.01 mole) of 1,1 - diphenyl - 3 - (6 - methoxy - 2 - naphthyl) - 1 - butene, 100 g. of ice-cold water and 400 ml. of acetic acid, 4.74 g. (0.03 mole) of potassium permanganate is added under stirring at 0 to 3°C. The mixture is filtered, alkalized, filtered and concentrated. The solution is acidified, and extracted with chloroform. The chloroform solution is dried and evaporated. 2 - (6 - methoxy - 2 - naphthyl) - propionic acid of melting point 153—155°C is obtained and the solid is recrystallized from a mixture of acetone and hexane.

Example 15

To a mixture of 3.4 g. (0.01 mole) 1,1 - diphenyl - 3 - (4 - iso - butylphenyl) - 1 - butene, 100 g. ice-cold water and 400 ml. of acetic acid 4.74 g. (0.03 mole) of potassium permanganate is added under stirring at 0 to 3°C. The mixture is worked up according to Example 14 and thus a product of melting point 75—76°C 2 - (4 - isobutylphenyl) - propionic is obtained, which may be recrystallised from petrolether.

Example 16

To a mixture of 4.72 g. 1,1 - diphenyl - 3 - [2 - (2,6 - dichloroanilino) - phenyl] - 1 - propene, 100 g. of ice-cold water and 400 ml. of acetic acid, 4.74 g. of potassium permanganate is added at 0 to 3°C under stirring. The mixture is worked up according to Example 14 and thus 2 - [2,6 - dichloroanilinophenyl] acetic acid is obtained.

Mp.: 156—158°C.

WHAT WE CLAIM IS:—

1. Process for the preparation of phenyl- and naphthyl-alkanoic acids of the general formula I

65

70

75

80

85

90

95

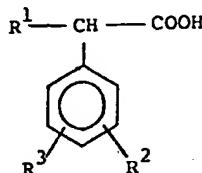
100

105

110

115

120



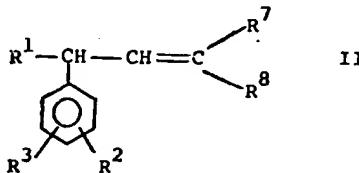
wherein

R¹ is hydrogen, C₁₋₄ alkyl, or C₇₋₁₀ aralkyl,

R² is hydrogen or halogen,

R³ is C₁₋₈ alkyl, C₇₋₁₀ aralkyl, phenyl, phenoxy, or —NH—R⁴— wherein R⁴ is a phenyl group optionally substituted with one or two halogen atoms; or

R² and R³ may together form a fused benzene ring which may optionally be substituted with a C₁₋₄ alkoxy group, which comprises oxidizing an alkene derivative of the general formula II



wherein

R¹, R², R³, R⁴, R⁵ and R⁶ are as defined above,

R⁷ and R⁸ are hydrogen, C₁₋₄ alkyl, C₅₋₆ cycloalkyl or phenyl or

R⁷ and R⁸ together with the carbon atom to which they are attached form a five or six-membered ring.

2. A process as claimed in claim 1, which comprises conducting the oxidation with potassium permanganate.

3. A process as claimed in claim 2 which comprises conducting the oxidation at 0 to 5°C in the presence of aqueous acetic acid.

4. A process as claimed in claim 3 wherein the oxidation is conducted at about 3°C.

5. A process as claimed in claim 2 wherein the oxidation is conducted at 0 to 50°C in the presence of sodium hydrogen carbonate and an organic solvent.

6. A process as claimed in claim 5 wherein said organic solvent is acetone.

7. A process as claimed in claim 2 wherein the oxidation is conducted in benzene in the presence of a crown complexing agent at 0 to 70°C.

40

8. A process as claimed in claim 1 wherein the oxidation is conducted with a mixture of alkali metal periodate and alkali metal permanganate.

45

9. A process as claimed in claim 8 wherein the oxidation is conducted in tert-butanol with a mixture of sodium periodate and potassium permanganate.

50

10. A process as claimed in claim 1 which comprises conducting the oxidation with chromium trioxide.

55

11. A process as claimed in claim 10 which comprises conducting the oxidation at 0 to 100°C in the presence of aqueous acetic acid.

55

12. A process according to claim 11 wherein the oxidation is performed at about 70°C.

60

13. A process according to claim 1 which comprises conducting the oxidation with oxygen saturated with ozone.

65

14. A process as claimed in claim 13 wherein the oxidation is conducted at -50 to -80°C.

70

15. A process as claimed in claim 13 or 14 wherein a solution of said compound is oxidised in a solvent selected from chloroform, methylene chloride, acetic acid and ethyl acetate.

75

16. A process as claimed in any of claims 13-15 wherein the intermediate ozonide is decomposed in the presence of hydrogen peroxide.

80

17. A process as claimed in claim 1, substantially as hereinbefore described.

75

18. A process as claimed in claim 1, substantially as hereinbefore described with reference to any one of the Examples.

80

19. Phenyl- and naphthyl-alkanoic acids of the general formula I whenever prepared by the process of any of the preceding claims.

For the Applicants,
FRANK B. DEHN & CO.,
Imperial House,
15-19 Kingsway,
London, WC2B 6UZ.